Pharmaceutical Process Development Using Computer Aided-Methods and Tools

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Publication date:
2015

Document Version
Peer reviewed version

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A majority of pharmaceutical production systems involve batch processes, which have served well the pharmaceutical industries as well as the regulatory bodies. Batch vessels provide the flexibility of handling different unit operations in a multipurpose plant. However, batch processes are not very efficient for product quality assurance and have a number of drawbacks. Over the last decade the regulatory bodies required the pharmaceutical companies to demonstrate more process understanding. Moreover, financial drivers require profit expectations to be met due to increasing R&D cost and high competition [2]. Consequently, pharmaceutical industry is expected to look for opportunities to rapidly evaluate the different alternatives for process improvement. To achieve this objective, Process Systems Engineering (PSE) methods and tools can have important roles to play, for example, (a) apply computer aided-methods and tools that are mature for other industries (such as chemical and petrochemical) also in solving problems in pharmaceutical industries, (b) in the evaluation and implementation of alternative solutions and/or designs and (c) to evaluate opportunities for continuous manufacturing [1-2].

An integrated computer-aided framework for the development of pharmaceutical processes has been developed to tackle key research areas for pharmaceutical processes (such as continuous processing, separation and reaction processes, solvent selection/recycle/optimization and process intensification/integration [3]). The objective of the framework is to improve pharmaceutical process operation/design and to evaluate opportunities for continuous manufacturing through better process understanding of pharmaceutical processes by using systematic model-based methods. Computer aided-methods and tools are important for such a framework as they can assist in solving various problems such as property prediction, mixture separation (ternary and binary azeotropic separations, separation sequence and type), solvent selection and process modeling and in providing data through knowledge libraries. The developed framework consists of four main parts: reaction mechanism identification, reaction analysis, separation synthesis and design and finally process simulation, evaluation, optimization and operation.

To extend the applicability of the framework a solvent swap method has been developed and implemented in a computer-aided tool. The solvent swap method is based on the method proposed by Gani et al. 2006 [4] and is treated as a special solvent selection problem with additional criteria consideration. The objective of the method is the quick and reliable identification of swap solvents which are suitable for the following process step and it can increase the process efficiency (minimize solvent and product loss and reduce energy demands).

The application of the proposed integrated framework with the added features will be highlighted through the BHC (Boots and Hoechst-Celanese) patented synthesis pathway for ibuprofen and the production of regioisomeric products through heck reactions [5]. The improved BHC synthesis of ibuprofen consists of three reaction steps [6] and it is used to verify the proposed integrated framework. Finally, the application of the solvent swap method using the computer-aided tool for both examples will be illustrated.

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